25 21. (New) The DNA sequence of claim 16, wherein said signal encoding sequence is the signal encoding sequence naturally associated with said mammalian milk protein promoter.

24 22. (New) The DNA sequence of claim 15, wherein said DNA sequence includes a transcriptional stop sequence.

27 23. (New) The DNA sequence of claim 22 wherein said stop sequence is derived from SV40 virus DNA.

28 24. (New) The DNA sequence of claim 23 wherein said stop sequence is contained in the polyadneylation sequence of SV40.

29 25. (New) The DNA sequence of claim 15 wherein said protein is human tissue plasminogen activator or hepatitis B surface antigen.

REMARKS

Claims 1,2, 4-9, 11 and 12-25 are pending. Claim 1 has been amended. However, the amendments to the claims have been made solely to expedite prosecution of the present application. New claims 12-25 have been added. Support for new claims 12-25 can be found throughout the present application as originally filed. No new matter has been added.

Rejection of Claims 1,2, 4-9 and 11 Under 35 U.S.C. §112, first paragraph

Claims 1, 2, 4-9, and 11 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the invention was filed, had possession of the claimed invention."

The claims have been rejected on the grounds that the written description and enablement requirements have not been fulfilled. The rejections are respectfully traversed. Applicant first discusses the written description rejection and then discusses the enablement rejection.

Written Description

The claims require a nucleic acid construct which includes the novel and unobvious combination of several art-known elements. One element is a milk protein promoter, e.g., a milk serum promoter or a casein promoter. It is important to keep in mind that the "genus" (and it is not even clear that referral to a small group of art-known entities is always a genus) of milk proteins is very small, it includes well less than approximately a dozen proteins. It contains two sub-genera, the milk serum (or whey) proteins, and the caseins. The milk serum protein genus is very small, and includes only approximately three proteins, WAP, α-lactalbumin, and β lactoglobin. Of these three, the sequence of the promoters of two (WAP and α-lactalbumin) were in the art at the time of filing. The casein genus is very small, it contains only about four proteins, α, β, κ, and λ casein. Of these, the sequence of the promoters of α, β, and λ casein were in the art at the time of filing. These are thus exceedingly well characterized genera.

It is also important to keep in mind that the claimed invention is not a new gene or new genetic entity purified from nature but rather a combination of art known elements. The recitation of such an element (and the specification goes well beyond merely naming the element) identifies and provides a written description of the element—it is not merely a wish, or a means of isolating the element. The fact pattern of the instant matter is entirely distinct, indeed essentially the polar opposite, of the fact pattern in cases like *University of California v. Eli Lilly*, 43 USPQ2d 1398 (Fed. Cir. 1997), wherein a patent or application recites the name of an element thought or known to exist in nature but where the element has never been isolated and structure is not provided anywhere, in the specification or in the art. Whether the written description requirement has been met must be answered in light of the requirements of the statute, in other words, is the description provided sufficient to convince one that the inventor was in possession of the invention. *Nothing more is required by the law.* In the case where the art knows the structure (and in this case the complete sequence of many if not most), the naming of the promoter and its gene is sufficient.

The written description guidelines, assuming they have relevance for this case, have been mis-applied to the instant claims. In the fourth paragraph of page 2 of the Office Action it is argued that the specification describes only a single promoter. As is discussed below, the specification does describe other promoters, art known promoters, and given the small size of the group, provides the required written description. On page 3 of the Office Action it is stated that a detailed description of the promoters is not provided and that one cannot describe what was not conceived, relying on *Fiers v. Revel* and *Amgen v. Chugai*. As is discussed in more detail below the invention in those cases was a new gene—the structure of which was not provided in the art or in the specification of the patents in suit. The Applicants' invention is not a new gene, but rather a novel and unobvious combination of elements, e.g., promoters, which were in the art at the time of filing. Thus, the problem which motivated the court in those cases, i.e., the lack of a detailed structural description, is simply not present in the instant claims.

The Applicants believe that the cases discussed above, and the PTO's written description guidelines, are misapplied in this case. Indeed, one could even argue that none of the

issues that call for application of the guidelines are present. Thus, the Guidelines are discussed in some detail below.

The Guidelines state that they were written to assist in the application of recent CAFC decisions which dealt with claims to particular types of genetic inventions. The Guidelines begin as follows:

> These **Written Description Guidelines** are intended to assist Office personnel in the examination of patent applications for compliance with the **written description** requirement of 35 U.S.C. 112, para. 1, in view of *University of California v. Eli Lilly* and the earlier cases *Fiers v. Revel*; and *Amgen, Inc. v. Chugai Pharmaceutical Co.* (citations omitted, emphasis in original).

Because of the importance of the *University of California v. Eli Lilly* to the Guidelines, it is discussed in detail here. In *University of California v. Eli Lilly*, the CAFC considered the written description requirement with regard to cDNA claims. The claims were to a novel species and to a novel genus. This was a "new gene" case. The specification of the patent in suit disclosed the DNA sequence of rat insulin and the amino acid sequence of human insulin. No nucleic acid sequence, restriction mapping, or other characterizing information was provided for an actual human nucleic acid sequence. No nucleic acid information for any other species (other than rat) was provided in the specification. The patent included generic claims which required mammalian and vertebrate cDNA's, though the specification provided only a single actual DNA sequence, that of rat insulin. A species claim which required a cDNA encoding human insulin was also presented, even though no actual human sequence, restriction mapping, or other characterizing information, was provided in the specification. The generic and species claims were held invalid.

The court reasoned as follows:

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. (emphasis added) Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

With regard to the human species claims the court held:

> Because the '525 specification provides only a general method of producing human insulin cDNA and a description of the human insulin A and B chain amino acid sequences that cDNA encodes, it does not provide a written description of human insulin cDNA. Accordingly, the district court did not err in concluding that claim 5 is invalid for failure to provide an adequate written description.

The court also found that the written description requirement was not met for the generic claims and it is discussed in some detail as to why it was not:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. (emphasis added).

While the patent in suit did not satisfy the written description requirement as set out by the CAFC, the claims in the instant matter do fulfil these requirements. The specification of the instant application teaches that milk promoters, e.g., milk serum promoters or casein promoters, are to be used in constructs of the inventions. Although no explicit recitation of casein promoters is provided it is noted that the "genus" of casein promoters is small, and includes only about 3 or 4 members. It has long been accepted that the naming of a generic term having a small number of species ordinarily constitutes sufficient written description of the species within it, see e.g., Bigham v. Godtfredsen, 8 USPQ 2d, 1266, 1268. With regard to milk serum promoters, which incidentally is also a very small genus, with about three species, the specification recites two species, WAP and α-lactalbumin. See page 2, lines 5-12, and page 4, lines 6-14, of the specification as originally filed for these written descriptions.

In the case of the WAP promoter, citations to references describing the promoters are provided in the specification. See page 5, lines 12-13. The references are Hennighausen and Sippel (1982) Eur. J. Biochem. 125: 131, and Campbell et al., (1984) Nuc. Acids Res. 12: 8685.

In the case of α-lactalbumin no reference was supplied, but the promoter was known in the art at the time of filing, see Qasba and Safaya (1984) Nature 308:377 (submitted herewith as Exhibit C).

In the case of casein promoters, no reference was supplied, but most or all of the casein promoters were known in the art at the time of filing, see Yu-Lee et al. (1986) *Nucleic Acid Res.* 14(4):1883-1901 (submitted herewith as Exhibit A)

In *University of California v. Eli Lilly*, the applicant merely named a gene it wanted to clone. The instant specification refers to known genera and species. The requirements enunciated in the case law are met.

In *University of California v. Eli Lilly*, the CAFC said that the description must be such that, "One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass." This requirement is met in the instant specification—the genus is small, and many of the members were well characterized in the art. Thus, one could certainly identify many of the species.

In *University of California v. Eli Lilly*, the CAFC said that "In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function." (emphasis added)" There is more in the instant case—the terms used in the specification have an inherent meaning conferred by the state of the art—they are a description which is directly tied to the known structure of known genes. The species are known and physically characterized genes.

A major holding in *University of California v. Eli Lilly*, was that purely functional terms were unacceptable:

> "One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is."

The terms here are far more than an indication of what the element does, or of how to obtain the element (though they are that as well). The species and genus terms used in the instant specification are a written description of art-known promoters.

The Guidelines recognize that the sufficiency of a written description must be determined on a case-by-case basis, "The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact." As is discussed above the facts are entirely different from those presented in *University of California v. Eli Lilly* and the earlier cases *Fiers v. Revel*; and *Amgen, Inc. v. Chugai Pharmaceutical Co.* (emphasis added)

The instant specification does not include extensive physical characterization of some of the promoters named. However, depending on the facts, and what is known in the art this is not always necessary. What is well known to one skilled in the art need not be disclosed. In section C the Guidelines provide that:

> What is well known to one skilled in the art need not be disclosed. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (emphasis in original).

This case is clearly one where structural details, known and published in scientific journals, need not be included.

Applicants note that no where in the case law, or guidelines, is there an absolute requirement for nucleic acid sequence – just as there is no absolute requirement for crystal structure in the case of a protein, or the exact bond angles and lengths in a nucleic acid or other molecule. There must be a case-by-case application of the standards.

In *University of California v. Eli Lilly*, it was emphasized that a written description inquiry is always very fact specific and that there are no absolute requirements.

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus... ("[I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'") (citations omitted). We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin. (emphasis added).

The Guidelines require that the Examiner review the entire application to determine what applicant has invented, the field of the invention and the level of predictability in the art. It provides:

> Prior to determining whether the claims satisfy the written description requirement, Office personnel should review the entire specification, including the specific embodiments, figures, sequence listings, and the claims, to understand what applicant has invented and the correspondence between what applicant has described, i.e., has possession of, and what applicant is claiming. Such a review should be conducted from the standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and, thus, the level of predictability in the art. (emphasis added).

The Guidelines require that the evaluation be conducted in view of the state of the art, and the art was in possession of milk specific promoters. The structures of the genes were known. Promoters are structures in the 5' flanking region of the gene. The

extraction of fragments containing the promoters was predictable at the time the invention was made.

In Section II B, the Guidelines require that the Examiner, for each claim, determine what the claim as a whole covers. Much if not all of this section IIB is directed to problems presented by claiming EST's or similar nucleic acids with open-ended language. It is irrelevant to the claimed subject matter, except to point out that in large part the guidelines are addressed to issues of novel nucleic acids and genes and the problems they represent, e.g., EST's or the novel specific/genes scenario from U.C. v. Lilly. All of which is largely irrelevant here.

Section II.C of the Guidelines require that the Examiner determine for each claimed species, whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. It provides:

> **Written description** may be satisfied through disclosure of relevant identifying characteristics, i.e., structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is well known to one skilled in the art need not be disclosed. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate **description** requirement is met. (bold emphasis in the original underlining added).

The Guidelines provide two ways of meeting the requirements of written description, by disclosing the "complete structure", as discussed in section II.C.1, or by the approach disabled in section II.C.2.

> If the complete structure is not disclosed, determine whether the specification discloses other relevant identifying characteristics, i.e., physical and/or chemical characteristics and/or functional characteristics coupled with a known or disclosed correlation between function and structure, sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. Disclosure of any combination of such identifying characteristics that would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. In such a case, a rejection for lack of written description under 35 U.S.C. 112 para. 1 must not be made.

The disclosure in the instant specification meets either standard. With regard to the standard of section II.C.1, one must first ask, in the context of the facts, the state of the art, predictability, and other relevant factors, what is a complete description? Is it the identification of a region on a chromosome, the determination of nucleic acid sequence or a restriction map, the disclosure of bond lengths and angles of every bond when in solution or crystallized? This must be answered in light of the requirements of the statute

– what is enough to convince one that the inventor was in possession of the invention. In the case where the art knows the structure (and in this case the complete sequence of many if not most), the naming of the promoter and its gene is sufficient.

Even if II.C.1 is not met the specification surely meets those of II.C.2, which relies on "relevant identifying characteristics". "Relevant identifying characteristics" are discussed in the guidelines at end note 17:

> 17. A "relevant identifying characteristic" is one that would provide evidence that applicant was in possession of what is claimed. For example, the presence of a restriction enzyme map of a gene may be relevant to a statement that the gene has been isolated. One skilled in the art could determine whether the gene disclosed was the same as or different than a gene isolated by another by comparing the restriction enzyme map. In contrast, evidence that the gene could be digested with a nuclease would not normally represent a relevant characteristic since any gene would be digested with a nuclease.

Surely the naming of a physically well characteristic gene meets this standard. One skilled in the art could, in the instant case, identify the gene.

The Guidelines provide examples of fact patterns which satisfy the written description requirement and examples which do not satisfy it. The Guidelines provide the following example which meets the requirement:

> An isolated double-stranded DNA consisting of (1) a single-stranded DNA which has a molecular size of 2.57 Kb and is derived from golden mosaic virus, and (2) a DNA complementary to said single-stranded DNA, giving the restriction endonuclease cleavage map shown in FIG.2(a) and having no Mbo I restriction endonuclease site.

The Guidelines provide the following example which does not meet the requirement.

> An isolated nucleotide sequence consisting of the sequence of the reverse transcript of a human mRNA, which mRNA encodes insulin.
>
> The specification in this example provides the coding sequence for rat insulin but not that for human insulin. The description for the reverse transcript of human mRNA is limited to its function, encoding human insulin, and to a method for isolating the claimed sequence from its natural source.

Applicants' situation, wherein art-known and well characterized genes are provided, seems much closer to the golden mosaic virus DNA example than to the situation in the rat-human insulin example. The rat-human insulin example provided in the Guidelines involves a species, human, the structure of which is unknown, it is not disclosed by the applicant or the art. Little, other than function, and perhaps how one might isolate it, is known. Naming the gene, e.g., WAP

might well teach how to obtain the promoter (indeed it does) but it also describes it.

In section D the Guidelines instruct the Examiner to determine for each claimed genus, determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed genus at the time the application was filed. The Guidelines provide:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by relevant identifying characteristics, i.e., structure or other physical and/or chemical characteristics, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" requires that the species which are expressly described be representative of the entire genus. Thus, when there is substantial variation within the genus, it may require a description of the various species which reflect the variation within the genus. For example, a broadly drawn claim to a specific gene from ruminant mammals may require a representative species from cattle, buffalo, bison, goat, deer, antelope, camel, giraffe and llama.
>
> What constitutes a "representative number" is an inverse function of the predictability of the art, as determined in II.A above. The number must be sufficient to reasonably identify the other members of genus. In an unpredictable art, adequate written description of a genus cannot be achieved by disclosing only one species within the genus. In fact, if the members of the genus are expected to vary widely in their identifying characteristics, such as structure and activity, written description for each member within the genus may be necessary.

The number is sufficient to reasonably identify the other members of the genus. As stated above the genera involved are very small and many if not the majority of the species have been sequenced. It is important to keep in mind that the genus of milk proteins is very small, it includes well less than approximately a dozen proteins. It contains two sub-genera, the milk serum (or whey) proteins, and the caseins. The milk serum protein genus is very small, and includes only approximately three proteins, WAP, α-lactalbumin, and β lactoglobin. Of these three, the sequence of the promoters of two (WAP and α-lactalbumin) were in the art at the time of filing. The casein genus is very small, it contains only about four proteins, α, β, κ, and λ casein. Of these, the sequence of the promoters of α, β, and λ casein were in the art at the time of filing. These are thus exceedingly well characterized genera.

Furthermore, the species do not vary widely in activity, in fact in the most critical sense they do not vary at all, they all drive milk-specific expression.

Significant structural similarities exist between at least some species, e.g., between the casein proteins. For example, Jones et al. (1985) compare rat β-casein and γ-casein and

report that the first 200 base pairs of the 5' flanking sequences of these genes are conserved. In particular, Jones et al. report that there are three regions within in the 5' flanking regions of β-casein and γ-casein which demonstrate greater than 70% homology. Jones et al. report that these regions, referred to as the proximal, medial and distal regions, span from –48 to –63, -106 to –119, and -130 to-165, respectively in the β-casein gene, and are in the same position ± three base pairs in the γ-casein gene. Moreover, one of these regions, the distal region, also has 90% homology with a known progesterone-binding site. Finally, Jones et al. state that "the resemblance between the proximal region to the CAAT sequence and the distal region to the progesterone binding site suggest possible functions" for these regions. Yu-Lee et al. (1986) also report that the first 200 base pairs of the 5' flanking region of the rat α-cascin, β-casein and γ-casein genes and the bovine α-casein gene are conserved. In particular, there are six regions of significant homology between these various casein genes in the 5' flanking region. Yu-Lee et al. also report that the conservation of the 5' flanking sequence of these genes is greater than those of both the mature coding region and intron regions of the genes.

There is also significant structural similarity between various species of WAP. For example, Campbell et al. (1984) report that the homology between murine and rat WAP extends 325 base pairs upstream from the transcription initiation sequence. Specifically, Campbell et al. report that there is approximately 83% homology between the murine and rat WAP genes. In addition, Campbell et al. report that in those 325 base pairs there is a region of 50 base pairs which are perfectly conserved between the murine and rat genes. Campbell et al. also report putative progesterone binding sites and glucocorticoid receptor binding sites located in the 5' flanking region of mouse and rat WAP.

Enablement

The Examiner also rejected the claims as lacking enablement.

Applicants respectfully traverse this rejection. Based on the disclosure of the present application and the knowledge in the art at the time of the present invention, one of ordinary skill in the art could practice the claimed invention without undue experimentation. In particular, there is sufficient guidance in the present application to enable a skilled artisan to make and use the DNA sequence as claimed. Applicants have provided sufficient guidance regarding both the specific structures of the claimed DNA sequence and methods of constructing a plasmid including these structures.

For example, at pages 3 and 4 of the present application, Applicants provide mammalian milk protein promoters which can be used in the claimed invention. Applicants describe mammalian milk promoters as being promoters naturally associated with proteins secreted into milk.

The promoter regions of milk proteins were known in the art at the time of invention. For example, the DNA sequence of murine whey acid protein (WAP) promoter was known in the art and was deposited as stated in the present application. Moreover, other milk protein promoter regions were known in the art at the time of invention. For example, Yu-Lee et al. (1986) *Nucleic Acid Res.* 14(4):1883-1901 (submitted herewith as Exhibit

A) describes the structure of the promoter region of rat α-casein and bovine α-cascin and compares these structures with those of rat β casein and rat γ casein. In addition, Campbell et al. (1984) *Nucleic Acid Res.* 12(22): 8585-8697 (submitted herewith as Exhibit B) describes the structure of rat and murine WAP promoter; Qasba and Safaya (1984) Nature 308:377 (submitted herewith as Exhibit C) disclose the complete nucleic acid sequence of the rat α-lactalbumin gene and identify the promoter region structures; Jones et al. (1985) *J. Biol. Chem.* 260:7042 (submitted herewith as Exhibit D) report the complete genomic sequence of the rat β casein gene including promoter-associated regions; Yu-Lee and Rosen (1983) *J. Biol. Chem.* 258:10794 (submitted herewith as Exhibit E) provide the complete genomic of the rat γ-cascin gene including promoter region structures; and Stewart et al. (1984) *Nucleic Acid Res.* 12:3895 (submitted herewith as Exhibit F) report the nucleotide sequence for bovine α-casein and identify the promoter region structures.

Applicants also provide signal sequences and termination sequences which can be included in the claimed DNA sequence. For example, page 6 of the present application provides that the signal sequence can be a signal sequence naturally associated with the protein to be secreted, a signal sequence naturally associated with the milk protein providing the promoter, or can be a signal sequence from another secreted protein other than the protein to be secreted or the milk protein. Various signal sequences were known in the art at the time of invention. For example, several of the references cited above also identify the signal sequence of the various milk proteins. In addition, the signal sequence of other secreted proteins were known in the art. This is also the case for termination sequences. Thus, Applicants have provided sufficient guidance of the various structures which can be used in the claimed DNA sequence.

Moreover, Applicants have also provided methods of making the claimed DNA sequence. For example, at pages 9-13 of the present application, Applicants provide methods of making a DNA construct which includes a gene encoding a protein under transcriptional control of a sequence of a milk protein promoter and a sequence which enables secretion of the protein. Specifically, Applicants describe the construction of a plasmid in which the gene encoding either human t-PA or hepatitis B surface antigen (Hbs) and its signal sequence are under transcriptional control of murine WAP promoter. In addition, Applicants also teach at page 13, lines 9-20, that the described plasmid DNA can be modified by excising the Hbs gene or tPA gene and replacing it with any desired gene using conventional methods. Applicants also teach that the signal sequence from either of the described plasmids can be left in the plasmid and a gene lacking such a sequence inserted downstream from it or that the signal sequence can be removed and the signal sequence of the substituted gene employed. Furthermore, the WAP promoter can be removed and replaced with a different milk protein promoter. As provided at page 7, lines 17-22 of the present application, all of these genetic manipulations of the plasmid can be carried out using routine methods such as those described in Maniatis et al., *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory, 1982). Thus, based on the teachings of the present application and the knowledge in the art at the time of invention, one of ordinary skill in the art could make and use the claimed DNA sequence without undue experimentation.

Applicants submit the First Declaration of Katherine Gordon (submitted herewith as Exhibit G) as evidence that the procedures described in the present application along with the knowledge in the art as of the effective filing date of the present application are sufficient to enable a skilled artisan to practice the claimed invention. In particular, several references are cited in the First Declaration of Katherine Gordon which demonstrate that techniques used to produce transgenic mammals were known in the art. Such references include Hammer et al. (1985) *Nature* 315:680 (submitted herewith as Exhibit H) which describes a detailed procedure for the microinjection of DNA into rabbits, sheep and pigs to make transgenic animals and Kraemer et al. *Gene Transfer into the Pronuclei of Cattle and Sheep Zygotes*, pp.221-222 (1985) (submitted herewith as Exhibit I) which shows that similar techniques were used to make with transgenic cows. Both of these references were published before the effective filing date of this application. References such as these provide comprehensive and detailed guidelines for the microinjection of foreign DNA into a variety of mammals and prove that the production of such transgenic mammals is enabled.

Moreover, Applicants submit the Second Declaration of Katherine Gordon to demonstrate that such procedures have been successfully used to produce recombinant proteins in the milk of transgenic animals. (submitted herewith as Exhibit J). This Declaration sets forth examples of the claimed transgenic mammals (e.g., mice and goats), generated by the disclosed methods, which express a recombinant protein in their mammary epithelial glands under lactating conditions, and secrete the recombinant protein into their milk. These results are also described in Gordon et al. (1987) *Bio/Technology* 5:1183 (submitted herewith as Exhibit K) and Gordon et al. (1991) *Bio/Technology* 9:835 (submitted herewith as Exhibit L). Thus, based on the knowledge in the art and the disclosure in the present application, there is sufficient guidance to enable a skilled artisan to make and use the claimed invention without undue experimentation.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 1, 2, 4-9 and 11 Under 35 U.S.C. §112, second paragraph

Claims 1, 2, 4-9 and 11 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner states that "[t]he claims are confusing as to 'a DNA sequence of a mammalian milk serum protein promoter."

Claim 1 has been amended to thereby obviate the Examiner's rejection of claim 1 and dependent claims 2, 4-9 and 11. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Conclusion

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 542-5070. Please apply any charges not covered, or any credits, to Deposit Account 06-1050.

Respectfully submitted,

Date: 28Oct99

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